UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,263	01/11/2006	Kersten M. Small	10738-50 PCT	5287

758 7590 02/06/2008

FENWICK & WEST LLP
SILICON VALLEY CENTER
801 CALIFORNIA STREET
MOUNTAIN VIEW, CA 94041

EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
02/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,263	SMALL ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,11-13 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,11-13 and 18* is/are rejected.

7)☒ Claim(s) *1,2;12 and 13* is/are objected to.

8)☒ Claim(s) *1-6,11-13 and 18* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

Claims 1-6, 11-13 and 18 are pending in the instant application.

Elections/Restrictions

In the 10/30/07 Office Action, Applicants were required to elect a single species of cardiovascular disease. Applicants' election of the species of heart failure in the reply filed on 11/28/07 is acknowledged.

Each of the claims encompasses the elected species.

Claims 1-6, 11-13 and 18 are under consideration, as they read upon the elected species of cardiovascular disease (heart failure).

Specification

The disclosure is objected to because of the following informalities:

A priority statement of the instant application's parent provisional and nonprovisional applications should be included in the first sentence of the specification or application data sheet. Specifically, the priority statement should indicate that the instant application is a 371 of PCT/US03/28135 (filed 9/9/03) which claims benefit of U.S. provisional application 60/409,167 (filed 9/9/02).

Appropriate correction is required.

Claim Objections

Claims 1, 2, 12 and 13 are objected to because of the following informalities:

(1) Claim 1 was amended on 10/11/06 to include a strikethrough over the space following "(β_1Arg389)" (i.e., "...adrenergic receptor (β_1Arg389)-in a sample..."). The strikethrough indicates the space has been deleted. This change is objected to because it results in a lack of space between "(β_1Arg389)" and the following word "in" (i.e., the amended claim now recites, "...adrenergic receptor (β_1Arg389)in a sample...").

(2) Claim 2 includes the recitation "the sample comprises blood sample". This recitation is objected to because it is missing an article (e.g., "a") between the words "comprises" and "blood" (e.g., "the sample comprises a blood sample...").

(3) Claim 12 has an extraneous space between "life-" and "style" (i.e., "life- style" should be "life-style").

(4) Claim 13 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants are required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Parent claim 6 recites, "the therapy regimen delays development of cardiovascular disease in the individual". Dependent claim 13 recites, "wherein progression or early death associated with the cardiovascular disease is delayed". Delaying progression associated with cardiovascular disease encompasses the same scope as delaying development of cardiovascular disease. Furthermore, delaying early death associated with cardiovascular disease is an inherent to delaying development of cardiovascular disease (i.e., cardiovascular disease leads to earlier death; therefore delaying such disease delays early death). As such, claim 13 fails to further limit the subject matter of parent claim 6.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-6, 11-13 and 18 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-6, 11-13 and 18 each encompass a method that is a judicial exception to 35 U.S.C. 101 (i.e., an abstract idea) and is not directed to a practical application of such judicial exception (e.g., because the claim does not require any physical

transformation and the invention does not produce a useful, concrete and tangible result). Specifically, the claims each encompass a method that is an abstract idea because each of the steps recited in the method is a mental step (i.e., no physical transformations are required by the method steps). "Obtaining information regarding the presence or absence of a deletion" in a protein (as recited in steps (a) and (b) of claim 1) does not require that the deletion is physically measured as part of the method. Furthermore, assessing risk (as in step (c) of claim 1) is solely a mental determination. Furthermore, "selecting a therapy" (as recited in each of dependent claims 6, 11, 12, 13 and 18) which is also solely a mental determination.

It is noted that claim 1 previously recited "detecting the presence or absence" of a deletion in a protein in each of steps (a) and (b). If the claims were amended, for example, to use this claim language, the claims would be directed to statutory subject matter, because the claimed method would require a physical detection step.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 11-13 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

(1) a method for assessment of risk for heart failure in an individual, comprising the steps of: (a) assaying for the presence or absence of a deletion of amino acids 322-325 in an α_{2C} adrenergic receptor (α_{2C}DEL322-325) in a sample from an individual; (b) assaying for the presence or absence of an arginine at position 389 of a β_1 adrenergic receptor (β_1Arg389) in a sample from an individual; and (c) if both a homozygous α_{2C}DEL322-325 polymorphism is present and a homozygous β_1Arg389 polymorphism is present, assessing that the individual is at increased risk for heart failure, and

(2) the method of (1) above, further comprising the step of selecting a therapy regimen for the individual based on the presence of both a homozygous α_{2C}DEL322-325 polymorphism is present and a homozygous β_1Arg389 polymorphism, wherein the therapy regimen delays development of heart failure in the individual, and

(3) the method of (2) above, wherein the therapy regimen comprises administration of an agonist of α_{2C}DEL322-325, an antagonist of β_1Arg389, or both;

does not reasonably provide enablement for

(4) a method for assessment of risk for heart failure in an individual, comprising the steps of: (a) obtaining information regarding the presence or absence of a deletion of amino acids 322-325 in an α_{2C} adrenergic receptor (α_{2C}DEL322-325) in a sample from an individual; (b) obtaining information regarding the presence or absence of an arginine at position 389 of a beta-1 adrenergic receptor (β_1Arg389) in a sample from an individual; and (c) if both α_{2C}DEL322-325 is present and β_1Arg389 is present, assessing that the individual is at increased risk for cardiovascular disease; or

(5) the method of (4) above, further comprising the step of selecting a therapy regimen for the individual based on the presence of both α_{2C}DEL322-325 polymorphism and β_1Arg389, wherein the therapy regimen delays development of cardiovascular disease in the individual, or

(6) The method of (5) above, wherein the therapy regiment comprises administration of agonists, and/or antagonists of α_{2C}DEL322-325 and β_1Arg389.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and

8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a method for cardiovascular disease assessment comprising a diagnosis of increased risk for cardiovascular disease based on the presence of two polymorphisms: α_{2C}DEL322-325 and β_1Arg389. The specification provides the following working example in support of the claimed invention (pg 19-27). The specification teaches that "Genotyping at these loci [α_{2C} and β_1] is carried out in 171 patients with heart failure and 193 control subjects". With regard to the diagnosis of "heart failure", the specification teaches that entry criteria was "ages 20-79, left ventricular ejection fractions (LVEF) of <35 percent, NYHA II-IV heart failure, and either idiopathic dilated cardiomyopathy or ischemic cardiomyopathy". The specification reports the following results: "In African-Americans, the adjusted odds of heart failure is 5.65 times higher in the α_{2C}Del322-325 homozygotes ... There is no risk with β1Arg389 alone. However, there is a marked increased risk of heart failure in individuals homozygous for both variants: adjusted odds ratio=10.11 ... This association holds with dilated and ischemic cardiomyopathy, and is independent of antecedent hypertension ... In Caucasians, the α_{2C}Del322-325 polymorphism is also associated with heart failure ... However, there are too few patients with both homozygous genotypes to adequately assess the risk". The results presented in the specification are confirmed by the publication of Small et al, October 10, 2002 (The New England Journal of Medicine. 347(15): 1135-1142; published after the claimed priority date of the instant application). Small teaches that the Del322-325 deletion "greatly decreases the function of these receptors (by approximately 85 percent) in transfected cells" and that the β_1Arg389 "results in an increase of approximately 200 percent in agonist-stimulated activity in transfected cells as compared with the β_1Gly389 receptor" (pg 1141).

The teachings of the specification and the relevant art support the enablement of a method for assessment of increased risk of heart disease in an individual based on the presence of both a homozygous α_{2C}Del322-325 polymorphism and a homozygous

β_1Arg389 mutation. However, the claimed methods lack enablement for the full scope of the claims for the following reasons.

(1) The claims encompass assessment of increased risk of any cardiovascular disease. In addition to heart failure, dependent claim 4 recites 12 other species of cardiovascular disease of varying etiology (e.g., stroke and shock). It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification whether the claimed method could be used to assess risk of any cardiovascular disease other than heart failure. There are no examples of risk assessment of a cardiovascular disease other than heart failure. The association of the presence of both homozygous polymorphisms with an increased risk of heart failure does not allow the skilled artisan to predict increased risk of any other species of cardiovascular disease. For example, with respect to hypertension, Li et al (2005) concludes, "our data in 246 homozygotes, 694 heterozygotes, and 518 noncarriers show no evidence either that Del322-325 allele is an independent predictor of hypertension or hypertensive heart disease in blacks or that this allele accelerates the age-dependent increase in BP [blood pressure]" (pg 1144 of Li et al, 2006. Hypertension. 47: 1140-1146). Prior to practicing the claimed method, the skilled artisan would need to engage in undue experimentation to confirm whether or not a representative number of cardiovascular diseases are associated with the presence of the polymorphism. Such experimentation would be undue in view of the breadth of the claim (covering a wide range of cardiovascular diseases of varying etiologies), the significant effort required for each association study, and the likelihood that even after significant work is performed that other species of cardiovascular will be found to have no association (as evidenced by the results of Li).

(2) The claims are not limited to assessment of increased risk based on the presence of homozygous polymorphisms. Instead, the claims encompass assessment based solely on detection of each polymorphism, which includes individuals that are heterozygous for each polymorphism (i.e., the claims encompass assessment of increased risk of heart failure (and other cardiovascular diseases) based on the

presence of heterozygous polymorphisms. However, the results presented in the specification and Small et al (2002) do not indicate that individuals that are heterozygous for either the α_{2C} or β_1 polymorphisms have an increased risk of heart failure or any other cardiovascular disease. As such, it would require undue experimentation to determine how to use the heterozygous presence of the polymorphisms to assess risk of heart failure (or other cardiovascular disease).

(3) Claim 11 also lacks enablement for the following reason. Claim 11 recites "[t]he method according to claim 6, wherein the therapy regimen comprises administration of agonists and/or antagonists of α_{2C}DEL322-325 and β_1Arg389". As described above, Small (2002) teaches that α_{2C}DEL322-325 has decreased receptor function and β_1Arg389 has increased receptor function. As such, the skilled artisan at the time of filing would predict that an agonist of α_{2C}DEL322-325 or an antagonist of β_1Arg389 could be selected for a therapy regimen that would delay development of cardiovascular disease. Such a prediction is supported by the subsequently published relevant art. Lobmeyer et al (2007) teaches that patients with the α_{2C}DEL322-325 and β_1Arg389 combination "had a significantly greater improvement in EF [ejection fraction of blood from the ventricle of the heart] with metroprolol [a selective β_1 blocker] compared to all other genotype combinations." (pg 281 of Lobmeyer et al, 2007. Pharmacogenetics and Genomics. 17(4): 277-282). As such the teachings of the specification and the relevant art support the enablement of a therapy regimen comprising administration of an agonist of α_{2C}DEL322-325, an antagonist of β_1Arg389, or both.

However, the scope of the phrase "agonists and/or antagonists" includes therapies that encompass administration of an antagonist of α_{2C}DEL322-325, an agonist of β_1Arg389, or both. However, the skilled artisan would predict that administration of an antagonist of α_{2C}DEL322-325, an agonist of β_1Arg389, or both would be detrimental because it would increase the activities associated with the polymorphisms, and would therefore not delay development of heart failure (or other cardiovascular disease). As such, it would require undue experimentation to determine how to use an antagonist of

α_{2C}DEL322-325, an agonist of β_1Arg389, or both in order delay development of heart failure (or other cardiovascular disease).

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 11-13 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it recites "a deletion of amino acids 322-355 in an alpha-2C adrenergic receptor (α_{2C}DEL322-325)". It is unclear whether the recited receptor has a deletion of residues 322-355 or 322-325.

Claim 11 is indefinite because the elements recited in the claims do not constitute proper Markush groups. The claims are indefinite in the alternative use of "and/or" because it is not clear what controls which of these limitations. See MPEP § 2173.05(h).

The remaining claims are rejected for depending from an indefinite claim.

Art of Note

The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon for a rejection are considered pertinent to the instant application:

a. Small et al. 2000. Journal of Biological Chemistry. 275(30): 23059-23064. In this article, Small et al first describe the α_{2C}DEL322-325 polymorphism. Small et al teach, "the Del322-325 polymorphism could conceivably predispose individuals to the development of disease" (pg 23063). Small et al do not teach that the specific combination of α_{2C}DEL322-325 and β_1Arg389 results in an increased risk of heart failure or any other cardiovascular disease.

b. Small et al. 2001. TRENDS in Pharmacological Sciences. 22(9): 471-477. In the review article, Small et al teach polymorphisms in the α_{2C} adrenoreceptor, including the DEL322-325 polymorphism. Small et al teach, "Given their frequencies, it is unlikely that any of these polymorphisms alone are a major risk factor for a disease, although this needs to be explicitly tested. However, in combination with other polymorphisms and environmental influences, they might represent important genetic components in complex diseases." (pg 476-477). Small et al do not teach that the specific combination of α_{2C}DEL322-325 and β_1Arg389 results in an increased risk of heart failure or any other cardiovascular disease.

c. Small et al. 2002 (published October 3, 2001). Methods of Enzymology. Vol 343: 459-475. In the review article, Small et al teach polymorphisms in the α_{2C} adrenoreceptor (including the DEL322-325 polymorphism) and in the β_1 adrenoreceptor (including the β_1Arg389). Small et al teach do not teach that the specific combination of α_{2C}DEL322-325 and β_1Arg389 results in an increased risk of heart failure or any other cardiovascular disease.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

zch

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646